REMARKS/ARGUMENTS

Support for the amendment to claims 1 and 15 is provided at p.7, lines 13-26 and p.11, lines 32-35. Support for the amendment to claim 11 is provided at p. 14, lines 5-26. Other amendments address issues of antecedent basis in response to the Examiner's comments below. The Examiner's paragraph numbering is used in responding to the Examiner's comments.

2. Hyperlinks have been deleted from the specification.

3. Claim 11 stands rejected for alleged lack of written description. The rejection is based on the specification providing teaching that analysis of ten percent of the genome requires a plurality of arrays. Applicant disagrees with the Examiner's position. The cited portion of the specification was intended to be an example. The number of arrays could be more or fewer than this example depending on the size of array and the density of probes. These factors are at the discretion of the experimenter. Nevertheless, the claim has been amended to specify that a plurality of arrays are used to moot the rejection.

5-6. The Examiner rejects a number of claim terms for alleged lack of antecedent basis. The claims have been amended to moot all these issues.

7-8. Claims 1, 2, 5-8 and 12-15 stand rejected as anticipated by Kozal. The Kozal reference discusses the same tiling method of analyzing polymorphisms as Cronin, which has been discussed and distinguished in previous prosecution. However, the Examiner is now proposing a new interpretation of the claims, whereby the requirements for two arrays (an array and a further array) two hybridization steps, two determining steps, and an estimating and reestimating step can be fulfilled by a single hybridization to a single array which is conceptually viewed as being two separate arrays. Although applicant disagrees that this a reasonable interpretation of the claims in view of the specification, the claims have nevertheless be amended to render the point moot. Claim 1 now explicitly states that the further array is designed based

on the estimated sequence determined from the estimating step performed on the primary array. It follows that the further array of the claim cannot be designed until the primary array has been hybridized to the target sequence and the target sequence estimated. By contrast, the array of the reference including all of its quadrants is designed at the same time. Thus, the reference does not disclose step (e) or any of the subsequent steps performed on the further array designed in step (e).

Claim 15 has been amended in similar fashion to claim 1 and also specifies that the designing step of a further iterations of the method is based on an estimate of the target nucleic acid from a previous cycle. The reference does not disclose designing an array based on an estimated sequence of the target nucleic acid determined from a previous array.

9. Claim 15 stands rejected as anticipated by Skiena. Skiena is said to disclose a method of analyzing a target nucleic acid comprising designing an array of probes complementary to an estimated sequence of the target nucleic acid wherein the array does not contain every possible probe of a given length (citing to claim 1, step (d)), hybridizing the array of probes to the target, determining a reestimated sequence of the target from the hybridization and repeating the designing hybridization and determining steps (citing to col. 4, lines 5-67 and claim 2).

The Skiena reference was extensively discussed and distinguished in previous prosecution including the appeal brief. The distinctions are not addressed by the Examiner, and will be repeated here with reference to the amended claims.

Skiena discusses a method of sequencing by hybridization that is intended to be general to any type of target sequence. Initially, the target sequence is hybridized to a universal sequencing array containing all probes of a given length (col. 6, lines 41-42). Subsets of positively and negatively hybridizing probes are then determined (col. 6, lines 45-48). A second array is then designed based on combinations of probes from the positively hybridizing subset (col. 6, lines 49-61). The hybridization is then repeated and subsets of positively and negatively hybridizing probes again determined (col. 6, line 61 to col. 7, line 5). The process is repeated until the cumulative hybridization data reveals the identity of the target sequence (col. 7, lines 9-15).

Claim 15 has been amended to specify a step of designing an array based on a target nucleic acid having a sequence, which is a variant of a reference sequence (as is also specified in claim 1). Skiena's method starts with a universal sequence array containing all probes of a given length and is intended to analyze a target without any prior knowledge of its identity. As discussed at greater length in the appeal brief, there was no motivation to alter Skiena's approach, in favor of designing an array to comprise a set of probes having complementarity to the known reference sequence. To do so would forfeit the utility of Skiena's own method for an analyzing any kind of target sequence. Moreover, the remaining steps in Skiena method which are intended for analyzing a target sequence without any prior knowledge as to its identity would seem unnecessarily complex for the simpler task of analyzing a variant of a known sequence.

In view of the above amendment, it is believed that additional differences between Skiena's method and claim 15 are moot. Nevertheless, applicant reiterates his position from the appeal brief that Skiena's does not discloses a step of estimating the sequence of a target nucleic acid. The Examiner takes the view that such is disclosed by step (d) of claim 1. However, step (d) does not recites "estimating" a sequence. Indeed the word "estimating" is not found in the entire Skiena patent. Rather claim 1(c) of Skiena requires identifying a set of hybridizing oligonucleotides, and step (d) recites selecting a second set of oligonucleotides based on the hybridization of the first set. Neither step (c) or (d) refers in any way to the reconstruction of an estimated sequence from the set of positively hybridizing oligonucleotides. To say that a set of positively hybridizing oligonucleotides itself constitutes a sequence without any attempt being made to orient the oligonucleotides with respect to each other would be akin to saying that a restriction mapping of a target reveals its sequence. Such would be abhorrent to usage in the art whereby a restriction map or set of hybridizing oligonucleotides may be regarded as being a fingerprint but is not a sequence.

Skiena also does not disclose reestimating the sequence of a target nucleic acid. The Examiner refers particularly to claim 2 of Skiena for such disclosure. However, the claim refers to "determining" the sequence of a target not reestimating it. In Skiena's initial iterations of his method, he does not disclose estimating a target sequence but rather identifies a subset of hybridizing probes. In the final step of Skiena's method he does not estimate a target sequence,

but rather determines the sequence uniquely. In Skiena's view at least, the determined sequence is correct and not an estimated, much less a reestimated sequence (col. 7, lines 12-15).

The Examiner's position may in part be based on the view that simply determining a set of hybridizing oligonucleotides itself constitutes "estimating the sequence of a target," under a broad interpretation of the claims which the Examiner feels entitled to make during prosecution. In response, applicant submits that the Examiner is not merely interpreting the claims broadly, but effectively reading out explicitly recited claim steps. The present claims recite separate steps of "determining the relative hybridization of the probes to the target nucleic acid," and "estimating the sequence of the target nucleic acid from the relative hybridization of the probes." Thus, to view "determining the relative hybridization of probes" as being equivalent to estimating a sequence effectively reads out the step of "estimating the sequence" from the claim.

In attempting to rebut applicant's position, the previous Examiner stated that Skiena "inherently teaches both steps of hybridization and estimation the sequence of a target nucleic acid (citing to col. 9, lines 33-49 and col. 4, lines 19-21) (final office action at p. 10). However, "[i]nherency ... *may not be established by probabilities or possibilities.*" *Mehl/Biophile v. Milgraum,* 52 USPQ2d 1303, 1305 (Fed. Cir. 1999) (emphasis supplied). "The mere fact that a certain thing *may* result from a given set of circumstances *is not sufficient* to establish inherency." *In re Rijckaert*, 28 USPQ2d 1955 (Fed. Cir. 1993) (emphasis supplied). Here, the previous Examiner's proposal of inherent disclosure of estimating a sequence relies on unsupported assumptions. Thus, when Skiena at col. 4, lines 19-21 refers to resolving "ambiguities" the Examiner is apparently supposing that Skiena has compiled a sequence from his hybridizing oligonucleotides, and is referring to ambiguities in that sequence. However, there is no basis for such an assumption, particularly, when in the example discussed at col. 6, lines 40 to col. 7, line 9, Skiena does not compile a sequence from hybridizing oligonucleotides until all of the hybridizations have completed. Instead, Skiena's "ambiguities" probably refer to ambiguities in the hybridization data due to the same oligonucleotide being complementary to multiple segments of a target sequence (see col. 4, lines 19-20). Col. 9, lines 33-49 of Skiena merely summarizes Table 2 and the number of iterations of Skiena's method needed to determine a sequence for various targets. This is every reason to suppose that these iterations refer to the

same process exemplified at col. 6, lines 40 to col. 7, line 9. As noted in this process, Skiena does not determine a sequence at any iteration except the last.

For these reasons, the Examiner has not established under principles of inherency that Skiena necessarily estimates or reestimates a sequence. Insofar as there is doubt, such doubt should inure to the benefit of appellant given that the burden of proof rests with the PTO. Accordingly, applicant maintains that Skiena does not teach "estimating," or "reestimating" a target sequence

Because Skiena does not disclose estimating or reestimating the sequence of a target nucleic acid, it follows that he also does not disclose designing an array of probes based on an estimated or reestimated sequence of a target nucleic acid.

For all of the above reasons, it is respectfully submitted that the rejection over Skiena should be withdrawn.

10. Claim 1-3, 5-15 stand rejected as anticipated by Chee. The Chee reference discusses the same method of analyzing nucleic acids discussed in Kozal and in Cronin (extensively discussed in previous prosecution). Claims 1-3 and 5-15 are distinguished over Chee for the same reasons as Kozal (see above).

11-12. Claim 4 stands rejected as obvious over Chee in view of Dietrich. Dietrich is cited as teaching comparison of human and primate sequences. Claim 4 is distinguished over Chee for at least the same reasons (discussed above) that claim 1 is distinguished over Kozal or Chee.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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